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Vaccination among HIV–infected, HIV-exposed uninfected and HIV-uninfected children: A systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness

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Abstract

Evidence-based approaches were used in making recommendations for vaccination against vaccine-preventable diseases for HIV-infected and HIV-exposed individuals but with limited substantiation. We conducted a systematic review and meta-analysis with randomised-controlled trials (RCTs), cohort and case-control studies that have efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes. Web of Science, Cochrane Library, PubMed and Scopus databases were searched for articles. Efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) against total vaccine serotype invasive pneumococcal disease was 32% in HIV-infected children and 78% among HIV-uninfected children. Vaccine effectiveness of Bacillus Calmette–Guérin vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59% protection in HIV-unexposed children. Likewise, HIV-uninfected children have better protection against invasive *Haemophilis influenzae* type b disease than the HIV-infected children. Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis compared to the non-exposed children. Children who are severely immunosuppressed are poorly protected against invasive pneumococcal diseases. HIV-infected children tend to have lesser vaccine protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than those who are immunosuppressed. The overall quality of the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This study reveals a dearth of efficacy and effectiveness studies among HIV-infected and exposed children.

***Keywords*:** HIV; vaccine-preventable diseases; sub-Saharan Africa; efficacy; effectiveness

Background

Immunisation is an essential aspect of preventive medicine and critical in reducing morbidity and mortality attributed to vaccine-preventable diseases in children, adolescents and adults.[1] The use of vaccines against various vaccine-preventable diseases is beneficial and an effective measure for protecting different age groups.[2,3] The vaccination rates of children remain insufficient for vaccine-preventable diseases in many developing countries with only 86% of infants vaccinated with three doses of diphtheria-tetanus-pertussis containing vaccine in 2016.[4] Low vaccination uptake rate results in an increase in unvaccinated and under-vaccinated human immunodeficiency virus (HIV)-infected and HIV-exposed children who are more likely to die from preventable diseases than their immunocompetent age mates.[5,6] Several care and treatment guidelines have identified vaccination as a crucial preventive strategy for people living with HIV[7,8] but information on the use of certain vaccines in this population are still scanty.[9]

Experts using evidenced-based approaches on the vaccination of immunocompromised individuals made specific recommendations for vaccination against major vaccine-preventable diseases for these patients but with limited proof.[8] Research gaps were also identified by this group for future investigation. One of these gaps was that of understanding the mediators of vaccine protection, adverse effects and basic aspects of the epidemiology of various vaccine-preventable diseases.[8]

Vaccines stimulate immunity that protects against specific disease-causing organisms. However, the effectiveness of different recommended vaccines in HIV-infected children may be reduced as a result of the decline in vaccine-induced antibodies.[10] The changing pattern of some vaccine-preventable diseases is poorly understood, and this changing pattern and epidemiology makes it important to better understand these diseases because of apparent resurgence and epidemics in future.[11] The suboptimal uptake of vaccines in sub-Saharan Africa coupled with the high HIV burden are risk factors that may facilitate future epidemics.[11,12]

Previous reviews on the efficacy and effectiveness of vaccines in HIV-infected and exposed children were not specific on the vaccine efficacy/effectiveness against disease outcomes and were not conducted as systematic reviews [13,14]. It is paramount to evaluate the available evidence by identifying high-quality literature and investigating the reliability of key findings as they relate to the pre-licensure efficacy and post-licensure effectiveness of vaccines in HIV-infected and HIV-exposed children compared to HIV unexposed children. The findings will provide the needed

evidence to guide healthcare policymakers, guideline developers, vaccinologists and healthcare workers in developing improved long-term vaccination strategies for HIV-infected children. Current and reliable evidence-based data on the efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children are also vital to inform a better understanding of the prevention and management of vaccine-preventable diseases in these children.

This systematic review and meta-analysis summarised available data from studies which have efficacy or effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes.

Results

Description of included studies

The flow diagram in Figure 1 shows the studies identified and selected for this review. We identified 725 publications through databases and clinical trial registry search with 479 studies after removal of duplicates. A total of 14 publications were included in this review. These publications comprise five randomised-controlled trials (RCTs),[15-19] six case-control studies,[20-25] one cohort study[26] and two cross-sectional studies[27,28]. Three of the included studies were publications from a particular South African trial that reported different vaccine efficacy outcomes.[15,17,18] The included studies were published from 1993 to 2017. All the included studies were conducted in sub-Saharan Africa with ten publications from South Africa, one each from Malawi, Angola and Zambia, and one multinational study conducted in Mali, Kenya and Ghana.

By outcomes, three studies reported rotavirus vaccine outcomes, six studies reported on pneumococcal vaccine, one study reported on Hib vaccine, two studies on Bacillus Calmette–Guérin (BCG) and two studies reported on Hepatitis B virus (HBV) vaccines (Table 1). Two studies compared vaccine strains with placebo among HIV-infected children while three studies compared vaccine strains with placebo among HIV-infected and HIV-unexposed children. Six studies compared HIV-infected children with HIV-unexposed children, while two studies compared HIV-exposed and uninfected children with HIV-unexposed children. In total, 66,220 children in comparative studies were involved in the included studies. The vaccine schedule and doses for the included studies were according to various national programme except for Madhi 2007[17] participants who were followed up for five years. Antiretroviral therapy (ART) usage varied between 22.5% and 67.0% among the HIV-infected children.

Figure 1: Flow diagram of the search and selection process for this review

Table 1: Characteristics of included studies

Quality of evidence

Risk of bias assessment of individual studies

Risk of bias assessment of the included studies is summarised separately for RCTs (Figure 2) and observational studies (Figure 3). All the studies except one contained at least one domain classified as high risk of bias or with no clear information.

Randomised trials

Only three RCTs were assessed.[15,16,19] Klugman 2003[15] was used in assessing two other included studies[17,18] since the study participants were the same for all three publications. There was insufficient information on random sequence selection in majority of the studies as shown in Figure 4. Allocation concealment, performance and detection biases were low for most of the studies. Steele 2011[19] had unclear risk of bias for most of the domains. Feikin 2012[16] had high risk of bias for reporting and other bias domains for not reporting all the pre-specified primary outcomes and having numerous limitations.

Figure 2: Risk of bias summary for the included randomised-controlled trials

Observational studies

All the observational studies had one high or unclear risk of bias across different domains except one study.[15,20,21,23-28] The reasons for the high risk of bias varied and ranged from the use of hospital control instead of community controls, imbalanced missing participant numbers and unmeasured confounders (Figure 5).

Figure 3: Risk of bias summary for the included observational studies

Figure 4: Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

Figure 5: Risk of bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

The quality of the evidence was also evaluated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Overall quality for the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This makes our confidence in the effect estimate to be moderate. With these results, we are confident that the true effect lies close to that of the estimate of the effect and does not require further research. See Summary of findings in Tables 2 and 3.

Table 2: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (RCTs)

Table 3: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (Observational studies)

Vaccine efficacy for vaccine-preventable diseases outcomes

Table 4 shows reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in trials for several outcomes. Vaccine efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) vs. placebo in preventing first episodes of invasive pneumococcal disease was 53% (95% CI 21 - 73) among HIV-infected children and 42% (95% CI -28 - 75) among HIV-uninfected children. Efficacy of PCV9 against total vaccine

serotype invasive pneumococcal disease was 32% (95% CI -14 - 60) in HIV-infected and 78% (95% CI 34 - 92) among HIV-uninfected children.

There was similar response among HIV-infected children who were given RIX4414 vaccine and those given placebo for prevention of acute rotavirus diarrhoea (RR= 1.00; 95% CI 0.26 - 3.78) (Table 5). The subset of HIV-infected children in a particular trial that compared pentavalent rotavirus vaccine (PRV) and placebo showed RR of 2.81 (95% CI 0.12 - 63.83) (Table 5).

Vaccine effectiveness for vaccine-preventable diseases outcomes

Table 6 reports vaccine effectiveness for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in observational studies for different outcomes. The pooled odds ratio (OR) of two studies on the effectiveness of HBV vaccines between HIV-infected and HIV-uninfected children was OR = 6.02 (95% CI 0.93 - 38.83*;* I^2 = 0.00%) (Table 5; Figure 6). Vaccine effectiveness of BCG vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59% protection in HIV-unexposed children (Table 5). Likewise, HIV-uninfected children have better protection against invasive Hib disease than the HIV-infected children (97% versus 44%). Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis comparable to the non-exposed children. The adjusted vaccine effectiveness of PCV13 against invasive pneumococcal disease was 78% (95% CI 46 to 91) in HIV-uninfected children, 17% (95% CI –304 - 80) in HIV-infected and –104% (95% CI –1433 - 73) among HIV-infected children who were severely immunosuppressed.

Figure: 6: Forest plot of comparison: Vaccine effectiveness comparing HIV-infected and HIV-uninfected - Hepatitis B vaccine, outcome: HBV/Hepatitis B vaccine

Table 4: Reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated vs. non-vaccinated participants in randomised-controlled trials

Table 5: Calculated vaccine efficacy and effectiveness for various vaccine outcomes

Table 6: Reported vaccine effectiveness against vaccine-preventable diseases in observational studies

Discussion

The findings of this systematic review show that various routine vaccines have varying levels of protective efficacy and effectiveness against different vaccine-preventable diseases among HIV-infected and HIV-exposed children. This study demonstrates that PCV9 and 13-valent pneumococcal conjugate vaccine (PCV13) vaccines are efficacious in preventing invasive pneumococcal disease, radiologically confirmed pneumonia and severe pneumonia.[15] PCV9 also reduced the incidence of antibiotic-resistant invasive and vaccine serotype pneumococcal disease in both HIV-infected and uninfected children.[15] However, PCV vaccines are less efficacious in preventing total vaccine serotype invasive pneumococcal disease in HIV-infected children compared to HIV-uninfected children.[16] Cohen et al. show that HIV-infected children have less protection against invasive pneumococcal disease when vaccinated with doses of PCV13.[21] HIV-infected children with severe immunosuppression are unprotected against invasive pneumococcal disease even at higher vaccine doses.[21]

Vaccine-efficacy studies show that RIX4414 and PRV do not have protective activities against acute rotavirus diarrhoea in HIV-infected children.[16,19] The poor efficacy of PRV in children living with HIV may largely be as a result of the small sample size of the HIV-infected children subset in a Kenyan trial.[16] However, Feikin et al. show that PRV efficacy against severe rotavirus gastroenteritis was 63.9% (95% CI −5.9-89.8) in a study with a large number of both HIV-infected and uninfected children in the second year of life and 83% in the first year of life. The study on RIX4414 shows that there was no significant difference in the incidence of rotavirus diarrhoea in the vaccine and placebo groups thereby deducing that the vaccine did not have any significant protective effect in HIV-infected children.[17] Monovalent rotavirus vaccines provided at least 40-60% protection against acute rotavirus gastroenteritis in both HIV-exposed uninfected and HIV-unexposed children but the effectiveness in HIV-infected children is not yet known.[23,26]

Vaccine-effectiveness studies show that Hib conjugate vaccine provided more than 50% protection against invasive Hib disease in HIV-uninfected children when compared to HIV-infected children.[24] Hib conjugate vaccine has a protective effect of 83% in preventing overall invasive Hib disease in among HIV-infected children and very useful.[26] A study among Zambian children shows that BCG has 59% protective effect against tuberculosis in HIV-uninfected children and none in HIV-infected children.[24] The findings of a case-control study among Brazilian children also allude to the fact that BCG does not protect against tuberculosis in immunodeficient HIV-infected children.[20]

Studies have shown that most of the vaccines included in this review are safe for use in all categories of children.[1,15,19,29,30] A number of reviews and safety studies on several routine vaccines among HIV-infected/exposed children and HIV-unexposed children show that there was no significant difference in these groups of children with respect to adverse events, serious adverse events and death.[26-33] Most of the serious adverse events and deaths were not vaccine related. Reviews also show that immune responses to primary vaccination in HIV-infected children were less likely compared to HIV-unexposed and HIV-exposed children and may require booster doses.[31-33]

There is a dearth of vaccine efficacy and effectiveness studies against vaccine-preventable diseases among HIV-infected and exposed children. This review shows that some efficacy studies have been done for PCV, BCG, rotavirus vaccines and Hib vaccines in HIV-infected children. There is a need to close the knowledge gap in relation to pre-licensure vaccine efficacy and post-licensure vaccine effectiveness against key vaccine-preventable diseases among these groups of children. Closing the gaps will entail conducting efficacy and effectiveness studies for several routine vaccines in HIV-infected and exposed children.[13] Use of BCG vaccines in HIV-infected children can lead to disseminated tuberculosis hence it is contraindicated in immunocompromised children. It is therefore, not advisable to do a BCG vaccine-efficacy study in these children.[34] BCG is safe in immunocompetent infants, however, immunocompromised infants are at high risk of developing disseminated BCG disease.[35]

It is estimated that 1.8M children are currently with living with HIV, most of them residing in sub-Saharan Africa.[36] This region also has the highest burden for most of the vaccine–preventable diseases such as tuberculosis etc.[37] It is therefore essential to have the children living with HIV and those exposed to HIV be protected against vaccine-preventable diseases despite possible lower vaccine efficacy among such populations.

Effectiveness research is essential and relevant for decision making by policy makers, treatment guideline researchers, vaccine development researchers and healthcare providers.[38] Vaccine-efficacy research is essential in making the necessary decisions to achieve the goals of the Global Health 2035 Grand Convergence.[39] The World Health Organization (WHO) has already recommended many vaccines for use in immunocompromised children especially those who have had exposure to HIV, however, most of these recommendations were made without specific vaccine-efficacy and effectiveness studies conducted in this population but rather from research findings on immunocompetent children or by using safety and immunogenicity

studies.[1,34] Advisory Committee on Immunization Practices (ACIP) also recommended various licensed vaccines for HIV-exposed children from birth through adolescence years except for BCG.[40] Knowing the vaccine efficacy and effectiveness against specific diseases will help steer guideline development and the need for better vaccines if the level of protection is low.

Strengths of this systematic review and meta-analysis are the comprehensive search conducted in several databases and the inclusion of several routine vaccines. This review also compiled evidence on efficacy and effectiveness of vaccines that could be of use in HIV-infected and HIV-exposed children especially in sub-Saharan Africa. The outcomes reported and pooled for this review were based on clinical features and diagnostic methods that has not changed significantly over the last two decades and as such not a limitation for this study. Lack of direct comparisons between HIV-infected and unexposed children with respect to various clinical cases of vaccine-preventable diseases limited straightforward grading of the evidence for clinical case outcomes. Only seven studies could be included in the meta-analysis due to lack of data information on some clinical outcomes and reported efficacy and effectiveness as described by the authors. Most of the included papers did not relate the immune status of the children with the efficacy of the administered vaccines except for Cohen et al. [21] which shows that lesser efficacy in children with severe immunosuppression. The included studies also did not report on the time interval between vaccination and the onset of the vaccine-preventable diseases.

Conclusions

Efficacy and effectiveness studies on vaccination exhibit possibilities for direct and indirect protection against various vaccine-preventable diseases among HIV-infected and HIV-exposed children. HIV-infected children tend to have less protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than the immunosuppressed ones. There is also a need to bridge the knowledge gap on vaccine efficacy and effectiveness of several routine vaccines in HIV-infected and exposed children. The study suggests that only a few vaccine-efficacy and effectiveness studies have been done in HIV-infected and exposed children previously.

Methods

Search strategy and selection criteria

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guideline.[41] The review was registered with PROSPERO (International prospective register of systematic reviews) (CRD42018095334).

Eligibility criteria

Inclusion criteria

We included randomised-controlled trials, cohort and case-control studies that included efficacy or effectiveness of vaccines in HIV-infected in comparison with HIV-exposed or HIV-uninfected children aged ≤ 18 years. The intervention group included those with standard vaccines or dosages while the comparison groups comprised of placebo, non-vaccinated groups, groups that were vaccinated with other control vaccines or other dosages among HIV-infected and HIV-exposed children. For case-control studies, cases were HIV-infected while controls were HIV-exposed uninfected and HIV-uninfected children.

The review planned to include the following licensed vaccines: Bacillus Calmette–Guérin, hepatitis B vaccine, oral polio vaccine, inactivated polio vaccine, diphtheria-tetanus-pertussis containing vaccines, *Haemophilus Influenzae* type B vaccine (Hib), pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV), yellow fever vaccine and measles-containing vaccines. These vaccines were chosen because they are the frequently used childhood vaccines in countries most affected by the HIV epidemic.

Exclusion criteria

Studies having population aged ≥ 18 years old individuals were excluded. We also excluded non-human studies and reviews. Most of the excluded studies reported outcomes such as level of antibodies, duplicates, reviews, studies not involving human, studies not reporting confirmed cases of vaccine-preventable diseases, reported vaccine efficacy and reported vaccine effectiveness.

Outcomes

The following were the outcome measures of interest:

1. Clinical and/or confirmed cases of vaccine-preventable diseases of interest.

2. Pooled/reported vaccine efficacy.
3. Pooled/reported vaccine effectiveness.

Data sources

One of the authors, OOA, searched the Web of Science, Cochrane Library, MEDLINE via PubMed and Scopus databases. Reference lists from identified papers and ClinicalTrials.gov trials registry platform were also checked. Relevant WHO position papers and documents on vaccines were also scrutinised. There was no language or date restriction.

Selection of studies

Two authors, OOA and DN, independently screened the search results using the abstract titles. They also independently went through the full text of potential studies to determine if the studies meet the inclusion criteria. Discrepancies in the selection process were resolved by consensus.

Data extraction

The two reviewers extracted data from selected articles using a pre-specified form. The extracts included information such as author, journal, year of publication, study design, country of study, participants' characteristics, intervention, comparator, type of vaccine and outcomes. Efficacy and effectiveness data were separately extracted for each vaccine group, target group (i.e. HIV-infected versus HIV-exposed / HIV-uninfected) and study type (interventional versus observational).

Quality assessment

The review quality assessment was guided by the use of Cochrane Collaboration's tool for assessing the risk of bias for included trials and the use of adapted Cochrane tool for observational studies.[42,43] Two authors, OOA and DN, independently assessed the methodological quality of all included studies that met the eligibility criteria. The researchers compared notes for each item and resolved discrepancies through discussion.

Synthesis of data

Synthesis of data was carried out using meta-analysis where applicable. Where meta-analysis was not possible, a narrative synthesis was used. We reported the dichotomous outcomes as risk ratios or odds ratio with their corresponding 95% confidence intervals (CI) while continuous outcomes were reported as mean differences.[44] We reported the vaccine effectiveness with the random-effects odds ratio (OR) using the formula: $(1 - OR) \times 100$ while vaccine efficacy was established with risk ratio (RR): $(1 - RR) \times 100$. The efficacy and

effectiveness of each vaccine in the intervention arm was compared with that of the control arm. We also planned to use funnel-plot regression to assess publication bias if we had up to ten studies per vaccine type. RevMan statistical software was used to do all calculations, the meta-analysis and to generate the forest plot.[45]

Sensitivity analysis

The certainty of the evidence regarding primary outcomes was determined by the use of the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[46] The term relative effect as used in GRADE refers to either Relative risk or Odds Ratio. The risk with placebo is an assumed risk or score in a group of people who do not receive the intervention. The risk with vaccine is a corresponding risk or score in a group of people who do receive the intervention. We planned to assess substantial heterogeneity if I^2 exceeded 50% and the meta-analysis had up to five studies and to perform subgroup analyses using pre-specified potential sources of heterogeneity such as: type of comparison (i.e. placebo or no vaccine), blinding of patients (only for trials); blinding of outcome assessors; and overall methodological quality.

Abbreviations

BCG: Bacillus Calmette–Guérin

CI: Confidence intervals

DTP: Diphtheria, tetanus and pertussis

HI: HIV-infected

HU: HIV-uninfected

Hib: *Haemophilus influenzae* type b

HIV: Human immunodeficiency virus

PCV9: 9-valent Pneumococcal conjugate vaccine

PCV13: 13-valent pneumococcal conjugate vaccine

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PRV: Pentavalent rotavirus

RCT: Randomised controlled trials

RV: Rotavirus

WHO: World Health Organization

Authors' contributions

OOA developed the protocol, search strategy, data analysis and manuscript preparation. OOA and DN did the screening, study selection and data extraction. OAU and CSW guided the development of the study. All authors were involved in the interpretation of results, revision and approval of the final review manuscript.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Vaccination among HIV–infected, HIV-exposed uninfected and HIV-uninfected children: A systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness

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Abstract

Evidence-based approaches were used in making recommendations for vaccination against vaccine-preventable diseases for HIV-infected and HIV-exposed individuals but with limited substantiation. We conducted a systematic review and meta-analysis with randomised-controlled trials (RCTs), cohort and case-control studies that have efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes. Web of Science, Cochrane Library, PubMed and Scopus databases were searched for articles. Efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) against total vaccine serotype invasive pneumococcal disease was 32% in HIV-infected children and 78% among HIV-uninfected children. Vaccine effectiveness of Bacillus Calmette–Guérin vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59% protection in HIV-unexposed children. Likewise, HIV-uninfected children have better protection against invasive *Haemophilis influenzae* type b disease than the HIV-infected children. Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis compared to the non-exposed children. Children who are severely immunosuppressed are poorly protected against invasive pneumococcal diseases. HIV-infected children tend to have lesser vaccine protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than those who are immunosuppressed. The overall quality of the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This study reveals a dearth of efficacy and effectiveness studies among HIV-infected and exposed children.

***Keywords*:** HIV; vaccine-preventable diseases; sub-Saharan Africa; efficacy; effectiveness

Background

Immunisation is an essential aspect of preventive medicine and critical in reducing morbidity and mortality attributed to vaccine-preventable diseases in children, adolescents and adults.[1] The use of vaccines against various vaccine-preventable diseases is beneficial and an effective measure for protecting different age groups.[2,3] The vaccination rates of children remain insufficient for vaccine-preventable diseases in many developing countries with only 86% of infants vaccinated with three doses of diphtheria-tetanus-pertussis containing vaccine in 2016.[4] Low vaccination uptake rate results in an increase in unvaccinated and under-vaccinated human immunodeficiency virus (HIV)-infected and HIV-exposed children who are more likely to die from preventable diseases than their immunocompetent age mates.[5,6] Several care and treatment guidelines have identified vaccination as a crucial preventive strategy for people living with HIV[7,8] but information on the use of certain vaccines in this population are still scanty.[9]

Experts using evidenced-based approaches on the vaccination of immunocompromised individuals made specific recommendations for vaccination against major vaccine-preventable diseases for these patients but with limited proof.[8] Research gaps were also identified by this group for future investigation. One of these gaps was that of understanding the mediators of vaccine protection, adverse effects and basic aspects of the epidemiology of various vaccine-preventable diseases.[8]

Vaccines stimulate immunity that protects against specific disease-causing organisms. However, the effectiveness of different recommended vaccines in HIV-infected children may be reduced as a result of the decline in vaccine-induced antibodies.[10] The changing pattern of some vaccine-preventable diseases is poorly understood, and this changing pattern and epidemiology makes it important to better understand these diseases because of apparent resurgence and epidemics in future.[11] The suboptimal uptake of vaccines in sub-Saharan Africa coupled with the high HIV burden are risk factors that may facilitate future epidemics.[11,12]

Previous reviews on the efficacy and effectiveness of vaccines in HIV-infected and exposed children were not specific on the vaccine efficacy/effectiveness against disease outcomes and were not conducted as systematic reviews [13,14]. It is paramount to evaluate the available evidence by identifying high-quality literature and investigating the reliability of key findings as they relate to the pre-licensure efficacy and post-licensure effectiveness of vaccines in HIV-infected and HIV-exposed children compared to HIV unexposed children. The findings will provide the needed

evidence to guide healthcare policymakers, guideline developers, vaccinologists and healthcare workers in developing improved long-term vaccination strategies for HIV-infected children. Current and reliable evidence-based data on the efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children are also vital to inform a better understanding of the prevention and management of vaccine-preventable diseases in these children.

This systematic review and meta-analysis summarised available data from studies which have efficacy or effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes.

Results

Description of included studies

The flow diagram in Figure 1 shows the studies identified and selected for this review. We identified 725 publications through databases and clinical trial registry search with 479 studies after removal of duplicates. A total of 14 publications were included in this review. These publications comprise five randomised-controlled trials (RCTs),[15-19] six case-control studies,[20-25] one cohort study[26] and two cross-sectional studies[27,28]. Three of the included studies were publications from a particular South African trial that reported different vaccine efficacy outcomes.[15,17,18] The included studies were published from 1993 to 2017. All the included studies were conducted in sub-Saharan Africa with ten publications from South Africa, one each from Malawi, Angola and Zambia, and one multinational study conducted in Mali, Kenya and Ghana. By outcomes, three studies reported rotavirus vaccine outcomes, six studies reported on pneumococcal vaccine, one study reported on Hib vaccine, two studies on Bacillus Calmette–Guérin (BCG) and two studies reported on Hepatitis B virus (HBV) vaccines (Table 1). Two studies compared vaccine strains with placebo among HIV-infected children while three studies compared vaccine strains with placebo among HIV-infected and HIV-unexposed children. Six studies compared HIV-infected children with HIV-unexposed children, while two studies compared HIV-exposed and uninfected children with HIV-unexposed children. In total, 66,220 children in comparative studies were involved in the included studies. The vaccine schedule and doses for the included studies were according to various national programme except for Madhi 2007[17] participants who were followed up for five years. Antiretroviral therapy (ART) usage varied between 22.5% and 67.0% among the HIV-infected children.

Figure 1: Flow diagram of the search and selection process for this review

Table 1: Characteristics of included studies

Quality of evidence

Risk of bias assessment of individual studies

Risk of bias assessment of the included studies is summarised separately for RCTs (Figure 2) and observational studies (Figure 3). All the studies except one contained at least one domain classified as high risk of bias or with no clear information.

Randomised trials

Only three RCTs were assessed.[15,16,19] Klugman 2003[15] was used in assessing two other included studies[17,18] since the study participants were the same for all three publications. There was insufficient information on random sequence selection in majority of the studies as shown in Figure 4. Allocation concealment, performance and detection biases were low for most of the studies. Steele 2011[19] had unclear risk of bias for most of the domains. Feikin 2012[16] had high risk of bias for reporting and other bias domains for not reporting all the pre-specified primary outcomes and having numerous limitations.

Figure 2: Risk of bias summary for the included randomised-controlled trials

Observational studies

All the observational studies had one high or unclear risk of bias across different domains except one study.[15,20,21,23-28] The reasons for the high risk of bias varied and ranged from the use of hospital control instead of community controls, imbalanced missing participant numbers and unmeasured confounders (Figure 5).

Figure 3: Risk of bias summary for the included observational studies

Figure 4: Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

Figure 5: Risk of bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

The quality of the evidence was also evaluated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Overall quality for the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This makes our confidence in the effect estimate to be moderate. With these results, we are confident that the true effect lies close to that of the estimate of the effect and does not require further research. See Summary of findings in Tables 2 and 3.

Table 2: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (RCTs)

Table 3: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (Observational studies)

Vaccine efficacy for vaccine-preventable diseases outcomes

Table 4 shows reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in trials for several outcomes. Vaccine efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) vs. placebo in preventing first episodes of invasive pneumococcal disease was 53% (95% CI 21 - 73) among HIV-infected children and 42% (95% CI -28 - 75) among HIV-uninfected children. Efficacy of PCV9 against total vaccine

serotype invasive pneumococcal disease was 32% (95% CI -14 - 60) in HIV-infected and 78% (95% CI 34 - 92) among HIV-uninfected children.

There was similar response among HIV-infected children who were given RIX4414 vaccine and those given placebo for prevention of acute rotavirus diarrhoea (RR= 1.00; 95% CI 0.26 - 3.78) (Table 5). The subset of HIV-infected children in a particular trial that compared pentavalent rotavirus vaccine (PRV) and placebo showed RR of 2.81 (95% CI 0.12 - 63.83) (Table 5).

Vaccine effectiveness for vaccine-preventable diseases outcomes

Table 6 reports vaccine effectiveness for vaccine-preventable diseases outcomes in vaccinated versus non-vaccinated participants in observational studies for different outcomes. The pooled odds ratio (OR) of two studies on the effectiveness of HBV vaccines between HIV-infected and HIV-uninfected children was OR = 6.02 (95% CI 0.93 - 38.83*;* I^2 = 0.00%) (Table 5; Figure 6). Vaccine effectiveness of BCG vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59 ~~%percent~~ protection in HIV-unexposed children (Table 5). Likewise, HIV-uninfected children have better protection against invasive Hib disease than the HIV-infected children (97% versus 44%). Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis comparable to the non-exposed children. The adjusted vaccine effectiveness of PCV13 against invasive pneumococcal disease was 78% (95% CI 46 to 91) in HIV-uninfected children, 17% (95% CI –304 - 80) in HIV-infected and –104% (95% CI –1433 - 73) among HIV-infected children who were severely immunosuppressed.

Figure: 6: Forest plot of comparison: Vaccine effectiveness comparing HIV-infected and HIV-uninfected - Hepatitis B vaccine, outcome: HBV/Hepatitis B vaccine

Table 4: Reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated vs. non-vaccinated participants in randomised-controlled trials

Table 5: Calculated vaccine efficacy and effectiveness for various vaccine outcomes

Table 6: Reported vaccine effectiveness against vaccine-preventable diseases in observational studies

Discussion

The findings of this systematic review show that various routine vaccines have varying levels of protective efficacy and effectiveness against different vaccine-preventable diseases among HIV-infected and HIV-exposed children. This study demonstrates that PCV9 and 13-valent pneumococcal conjugate vaccine (PCV13) vaccines are efficacious in preventing invasive pneumococcal disease, radiologically confirmed pneumonia and severe pneumonia.[15] PCV9 also reduced the incidence of antibiotic-resistant invasive and vaccine serotype pneumococcal disease in both HIV-infected and uninfected children.[15] However, PCV vaccines are less efficacious in preventing total vaccine serotype invasive pneumococcal disease in HIV-infected children compared to HIV-uninfected children.[16] Cohen et al. show that HIV-infected children have less protection against invasive pneumococcal disease when vaccinated with doses of PCV13.[21] HIV-infected children with severe immunosuppression are unprotected against invasive pneumococcal disease even at higher vaccine doses.[21]

Vaccine-efficacy studies show that RIX4414 and PRV do not have protective activities against acute rotavirus diarrhoea in HIV-infected children.[16,19] The poor efficacy of PRV in children living with HIV may largely be as a result of the small sample size of the HIV-infected children subset in a Kenyan trial.[16] However, Feikin et al. show that PRV efficacy against severe rotavirus gastroenteritis was 63.9% (95% CI −5.9-89.8) in a study with a large number of both HIV-infected and uninfected children in the second year of life and 83% in the first year of life. The study on RIX4414 shows that there was no significant difference in the incidence of rotavirus diarrhoea in the vaccine and placebo groups thereby deducing that the vaccine did not have any significant protective effect in HIV-infected children.[17] Monovalent rotavirus vaccines provided at least 40-60% ~~percent~~ protection against acute rotavirus gastroenteritis in both HIV-exposed uninfected and HIV-unexposed children but the effectiveness in HIV-infected children is not yet known.[23,26]

Vaccine-effectiveness studies show that Hib conjugate vaccine provided more than 50% protection against invasive Hib disease in HIV-uninfected children when compared to HIV-infected children.[24] Hib conjugate vaccine has a protective effect of 83% in preventing overall invasive Hib disease in among HIV-infected children and very useful.[26] A study among Zambian children shows that BCG has 59% protective effect against tuberculosis in HIV-uninfected children and none in HIV-infected children.[24] The findings of a case-control study among Brazilian children also allude to the fact that BCG does not protect against tuberculosis in immunodeficient HIV-infected children.[20]

Studies have shown that most of the vaccines included in this review are safe for use in all categories of children.[1,15,19,29,30] A number of reviews and safety studies on several routine vaccines among HIV-infected/exposed children and HIV-unexposed children show that there was no significant difference in these groups of children with respect to adverse events, serious adverse events and death.[26-33] Most of the serious adverse events and deaths were not vaccine related. Reviews also show that immune responses to primary vaccination in HIV-infected children were less likely compared to HIV-unexposed and HIV-exposed children and may require booster doses.[31-33]

There is a dearth of vaccine efficacy and effectiveness studies against vaccine-preventable diseases among HIV-infected and exposed children. This review shows that some efficacy studies have been done for PCV, BCG, rotavirus vaccines and Hib vaccines in HIV-infected children. There is a need to close the knowledge gap in relation to pre-licensure vaccine efficacy and post-licensure vaccine effectiveness against key vaccine-preventable diseases among these groups of children. Closing the gaps will entail conducting efficacy and effectiveness studies for several routine vaccines in HIV-infected and exposed children.[13] Use of BCG vaccines in HIV-infected children can lead to disseminated tuberculosis hence it is contraindicated in immunocompromised children. It is therefore, not advisable to do a BCG vaccine-efficacy study in these children.[34] BCG is safe in immunocompetent infants, however, immunocompromised infants are at high risk of developing disseminated BCG disease.[35]

It is estimated that 1.8M children are currently with living with HIV, most of them residing in sub-Saharan Africa.[36] This region also has the highest burden for most of the vaccine–preventable diseases such as tuberculosis etc.[37] It is therefore essential to have the children living with HIV and those exposed to HIV be protected against vaccine-preventable diseases despite possible lower vaccine efficacy among such populations.

Effectiveness research is essential and relevant for decision making by policy makers, treatment guideline researchers, vaccine development researchers and healthcare providers.[38] Vaccine-efficacy research is essential in making the necessary decisions to achieve the goals of the Global Health 2035 Grand Convergence.[39] The World Health Organization (WHO) has already recommended many vaccines for use in immunocompromised children especially those who have had exposure to HIV, however, most of these recommendations were made without specific vaccine-efficacy and effectiveness studies conducted in this population but rather from research findings on immunocompetent children or by using safety and immunogenicity

studies.[1,34] Advisory Committee on Immunization Practices (ACIP) also recommended various licensed vaccines for HIV-exposed children from birth through adolescence years except for BCG.[40] Knowing the vaccine efficacy and effectiveness against specific diseases will help steer guideline development and the need for better vaccines if the level of protection is low.

Strengths of this systematic review and meta-analysis are the comprehensive search conducted in several databases and the inclusion of several routine vaccines. This review also compiled evidence on efficacy and effectiveness of vaccines that could be of use in HIV-infected and HIV-exposed children especially in sub-Saharan Africa. The outcomes reported and pooled for this review were based on clinical features and diagnostic methods that has not changed significantly over the last two decades and as such not a limitation for this study. -Lack of direct comparisons between HIV-infected and unexposed children with respect to various clinical cases of vaccine-preventable diseases limited straightforward grading of the evidence for clinical case outcomes. Only seven studies could be included in the meta-analysis due to lack of data information on some clinical outcomes and reported efficacy and effectiveness as described by the authors. Most of the included papers did not relate the immune status of the children with the efficacy of the administered vaccines except for Cohen et al. [21] which shows that lesser efficacy in children with severe immunosuppression. The included studies also did not report on the time interval between vaccination and the onset of the vaccine-preventable diseases.

Conclusions

Efficacy and effectiveness studies on vaccination exhibit possibilities for direct and indirect protection against various vaccine-preventable diseases among HIV-infected and HIV-exposed children. HIV-infected children tend to have less protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than the immunosuppressed ones. There is also a need to bridge the knowledge gap on vaccine efficacy and effectiveness of several routine vaccines in HIV-infected and exposed children. Thecis study showssuggests that only a few vaccine-efficacy and effectiveness studies have been done in HIV-infected and exposed children previously.

Methods

Search strategy and selection criteria

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guideline.[41] The review was registered with PROSPERO (International prospective register of systematic reviews) (CRD42018095334).

Eligibility criteria

Inclusion criteria

We included randomised-controlled trials, cohort and case-control studies that included efficacy or effectiveness of vaccines in HIV-infected in comparison with HIV-exposed or HIV-uninfected children aged ≤ 18 years. The intervention group included those with standard vaccines or dosages while the comparison groups comprised of placebo, non-vaccinated groups, groups that were vaccinated with other control vaccines or other dosages among HIV-infected and HIV-exposed children. For case-control studies, cases were HIV-infected while controls were HIV-exposed uninfected and HIV-uninfected children.

The review planned to include the following licensed vaccines: Bacillus Calmette–Guérin, hepatitis B vaccine, oral polio vaccine, inactivated polio vaccine, diphtheria-tetanus-pertussis containing vaccines, *Haemophilus Influenzae* type B vaccine (Hib), pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV), yellow fever vaccine and measles-containing vaccines. These vaccines were chosen because they are the frequently used childhood vaccines in countries most affected by the HIV epidemic.

Exclusion criteria

Studies having population aged ≥ 18 years old individuals were excluded. We also excluded non-human studies and reviews. Most of the excluded studies reported outcomes such as level of antibodies, duplicates, reviews, studies not involving human, studies not reporting confirmed cases of vaccine-preventable diseases, reported vaccine efficacy and reported vaccine effectiveness.

Outcomes

The following were the outcome measures of interest:

1. Clinical and/or confirmed cases of vaccine-preventable diseases of interest.

2. Pooled/reported vaccine efficacy.
3. Pooled/reported vaccine effectiveness.

Data sources

One of the authors, OOA, searched the Web of Science, Cochrane Library, MEDLINE via PubMed and Scopus databases. Reference lists from identified papers and ClinicalTrials.gov trials registry platform were also checked. Relevant WHO position papers and documents on vaccines were also scrutinised. There was no language or date restriction.

Selection of studies

Two authors, OOA and DN, independently screened the search results using the abstract titles. They also independently went through the full text of potential studies to determine if the studies meet the inclusion criteria. Discrepancies in the selection process were resolved by consensus.

Data extraction

The two reviewers extracted data from selected articles using a pre-specified form. The extracts included information such as author, journal, year of publication, study design, country of study, participants' characteristics, intervention, comparator, type of vaccine and outcomes. Efficacy and effectiveness data were separately extracted for each vaccine group, target group (i.e. HIV-infected versus HIV-exposed / HIV-uninfected) and study type (interventional versus observational).

Quality assessment

The review quality assessment was guided by the use of Cochrane Collaboration's tool for assessing the risk of bias for included trials and the use of adapted Cochrane tool for observational studies.[42,43] Two authors, OOA and DN, independently assessed the methodological quality of all included studies that met the eligibility criteria. The researchers compared notes for each item and resolved discrepancies through discussion.

Synthesis of data

Synthesis of data was carried out using meta-analysis where applicable. Where meta-analysis was not possible, a narrative synthesis was used. We reported the dichotomous outcomes as risk ratios or odds ratio with their corresponding 95% confidence intervals (CI) while continuous outcomes were reported as mean differences.[44] We reported the vaccine effectiveness with the random-effects odds ratio (OR) using the formula: $(1 - OR) \times 100$ while vaccine efficacy was established with risk ratio (RR): $(1 - RR) \times 100$. The efficacy and

effectiveness of each vaccine in the intervention arm was compared with that of the control arm. We also planned to use funnel-plot regression to assess publication bias if we had up to ten studies per vaccine type. RevMan statistical software was used to do all calculations, the meta-analysis and to generate the forest plot.[45]

Sensitivity analysis

The certainty of the evidence regarding primary outcomes was determined by the use of the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[46] The term relative effect as used in GRADE refers to either Relative risk or Odds Ratio. The risk with placebo is an assumed risk or score in a group of people who do not receive the intervention. The risk with vaccine is a corresponding risk or score in a group of people who do receive the intervention. We planned to assess substantial heterogeneity if I^2 exceeded 50% and the meta-analysis had up to five studies and to perform subgroup analyses using pre-specified potential sources of heterogeneity such as: type of comparison (i.e. placebo or no vaccine), blinding of patients (only for trials); blinding of outcome assessors; and overall methodological quality.

Abbreviations

BCG: Bacillus Calmette–Guérin
CI: Confidence intervals
DTP: Diphtheria, tetanus and pertussis
HI: HIV-infected
HU: HIV-uninfected
Hib: *Haemophilus influenzae* type b
HIV: Human immunodeficiency virus
PCV9: 9-valent Pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRV: Pentavalent rotavirus
RCT: Randomised controlled trials
RV: Rotavirus
WHO: World Health Organization

Authors' contributions

OOA developed the protocol, search strategy, data analysis and manuscript preparation. OOA and DN did the screening, study selection and data extraction. OAU and CSW guided the development of the study. All authors were involved in the interpretation of results, revision and approval of the final review manuscript.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Figure 1

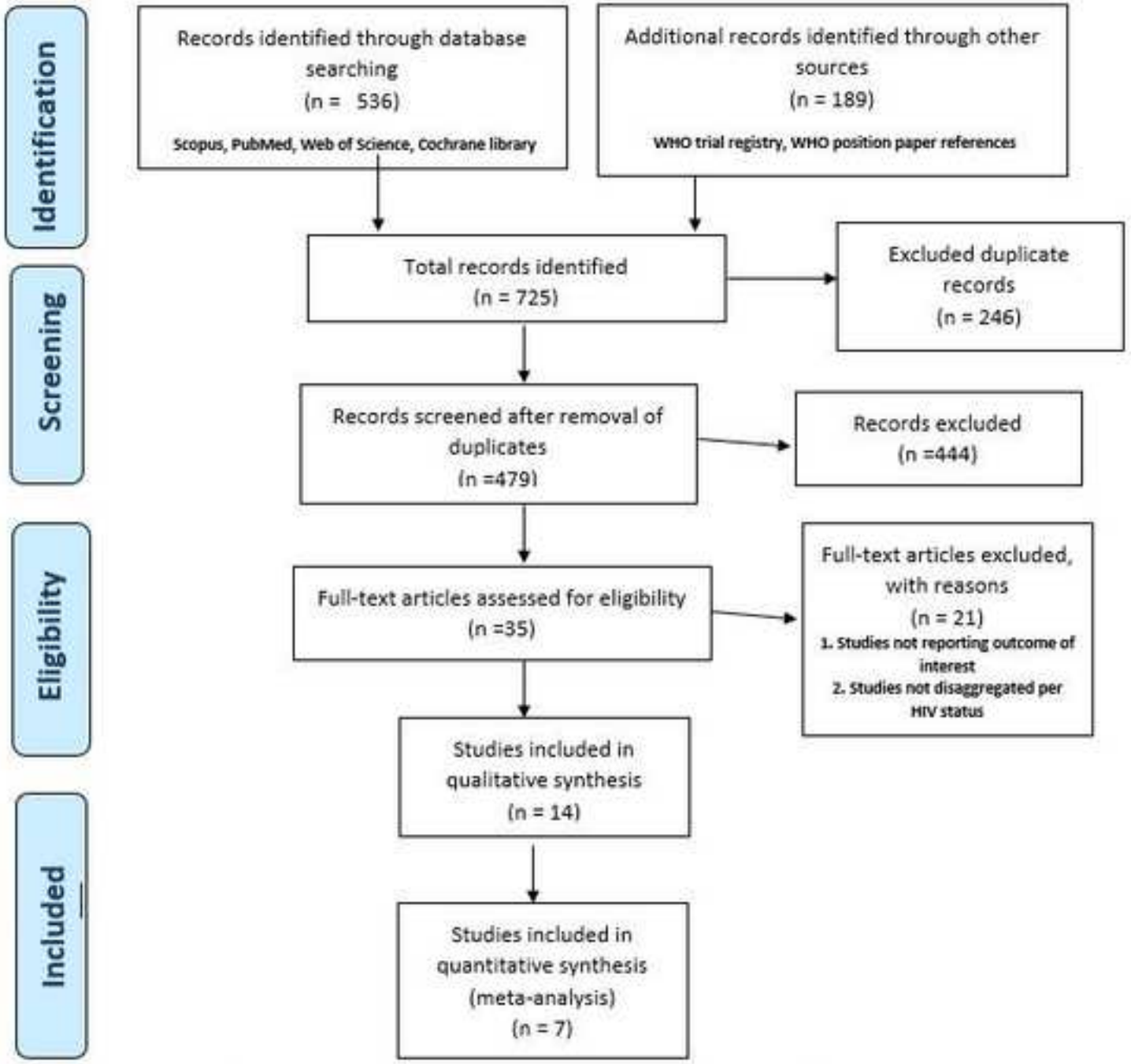

Figure 1: Flow diagram of the search and selection process for this review

Figure 2 revised

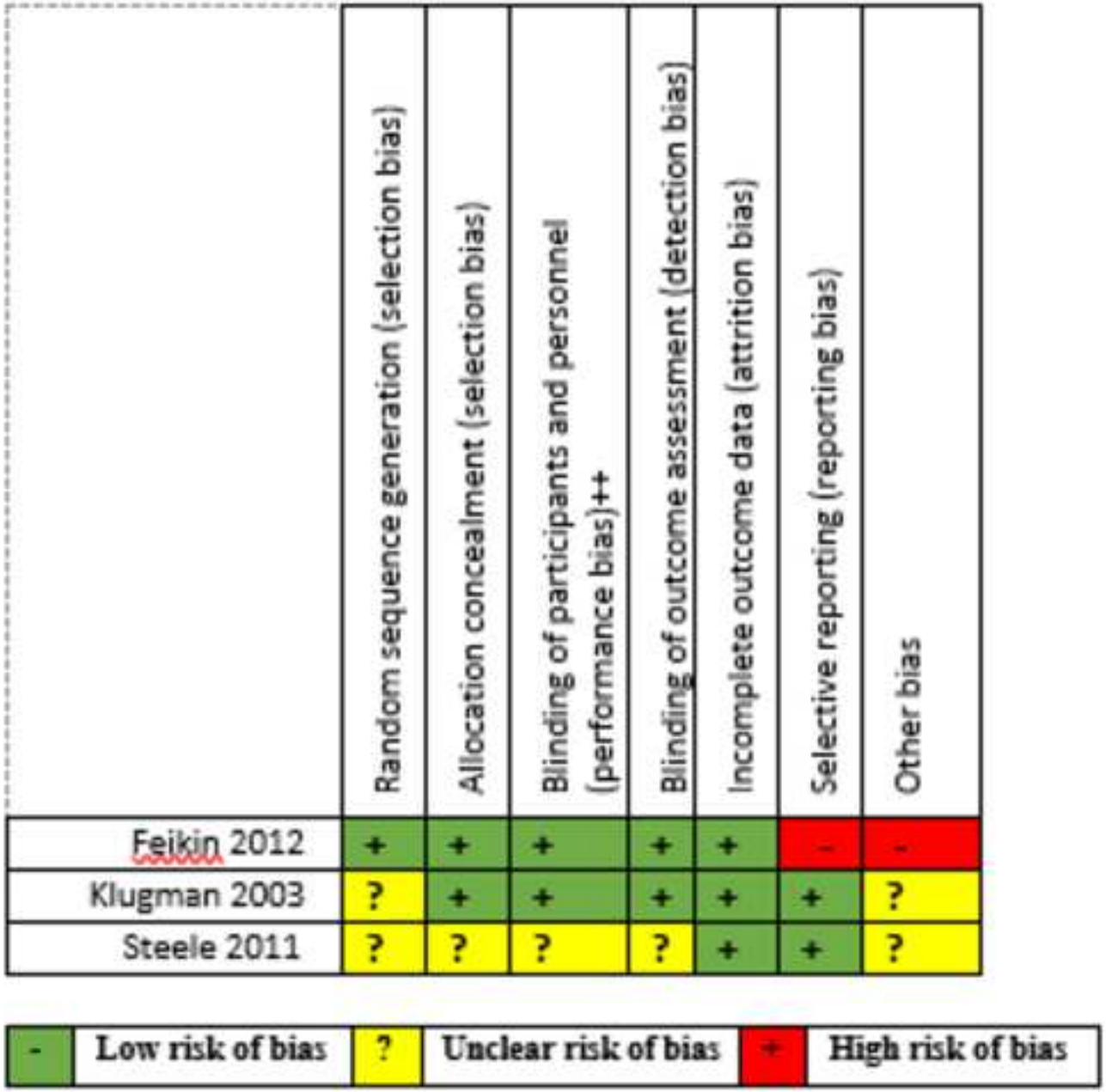

Figure 2: Risk of bias summary for the included randomised-controlled trials

Figure 3 revised

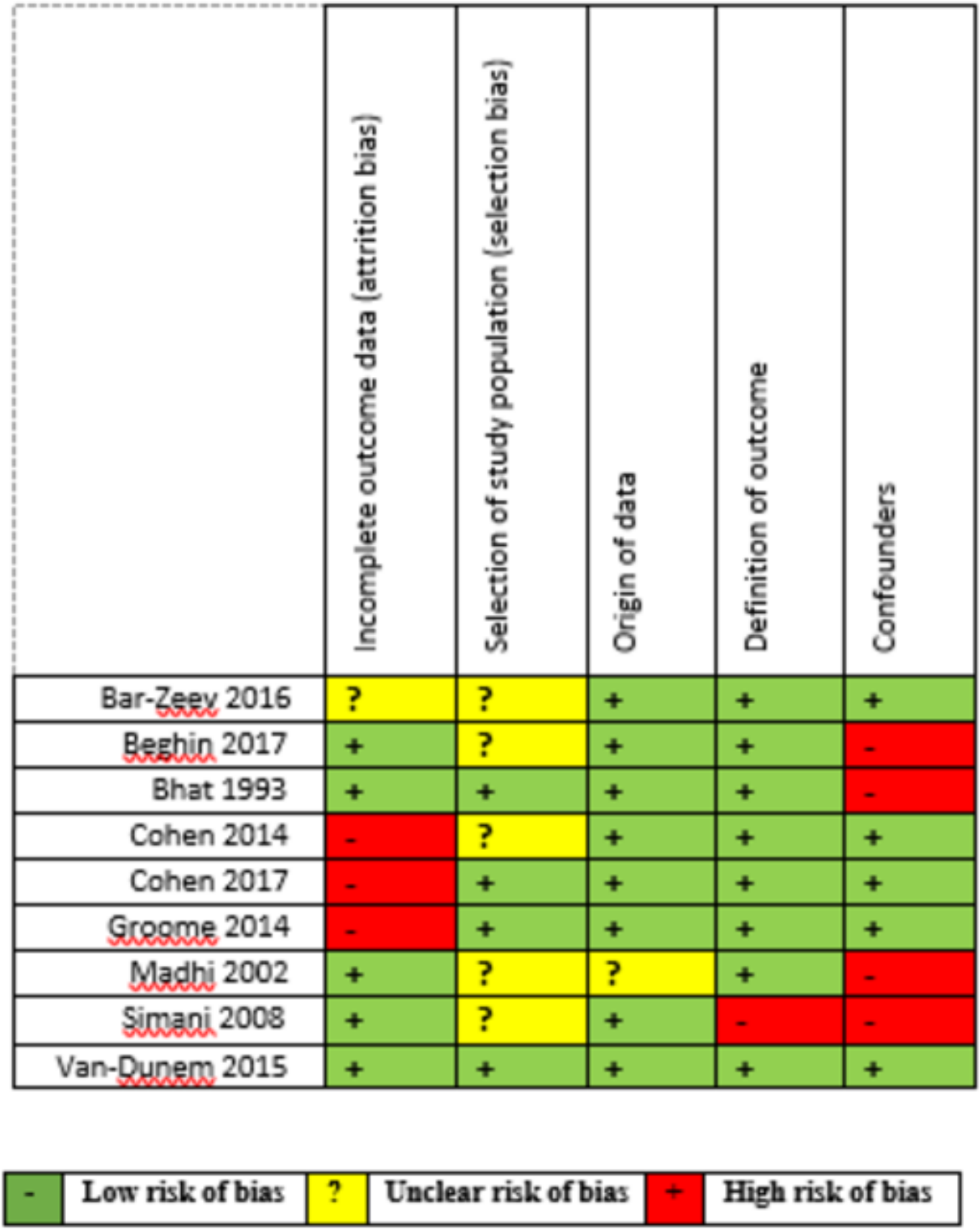

Figure 3: Risk of bias summary for the included observational studies

Figure 4

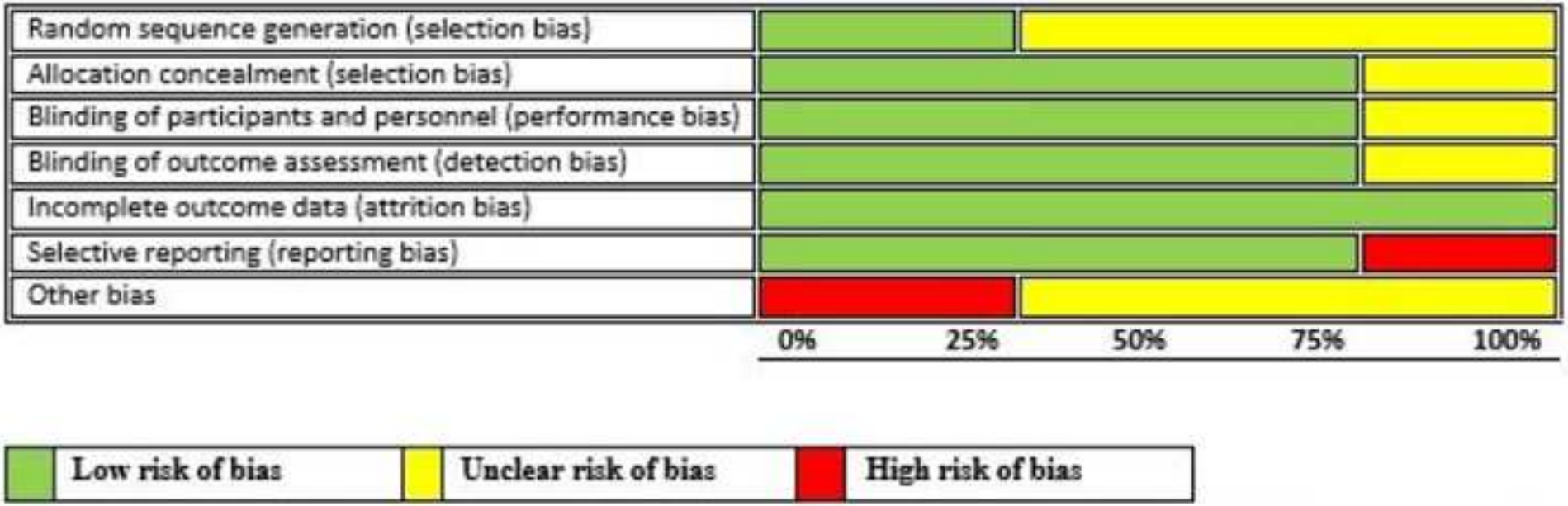

Figure 4: Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

Figure 5

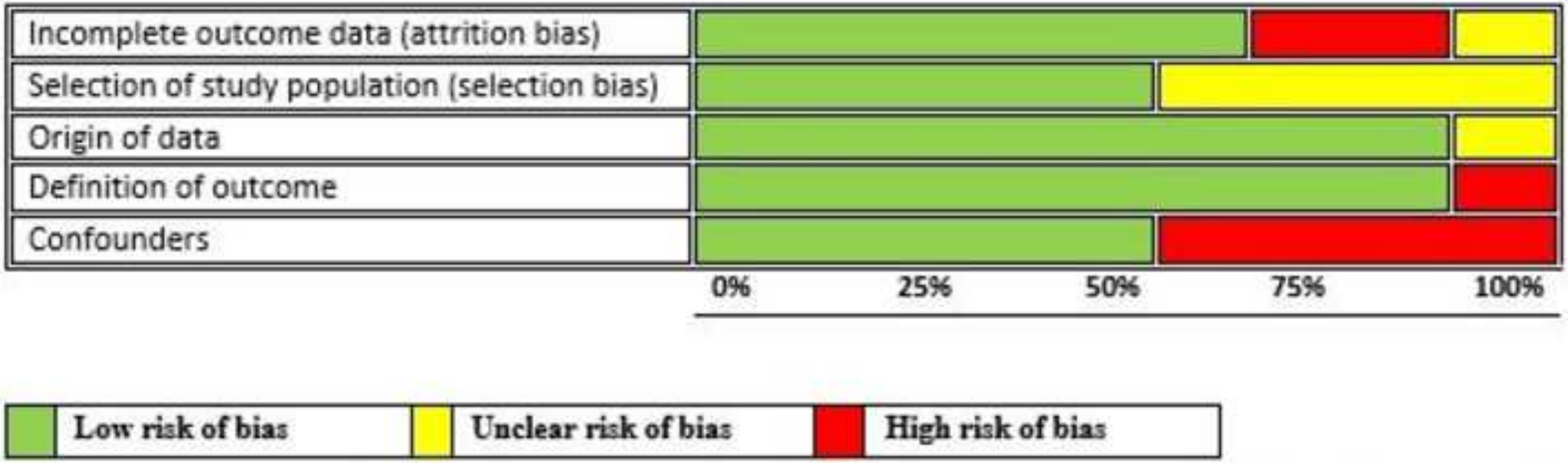

Figure 5: Risk of bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

Figure 6

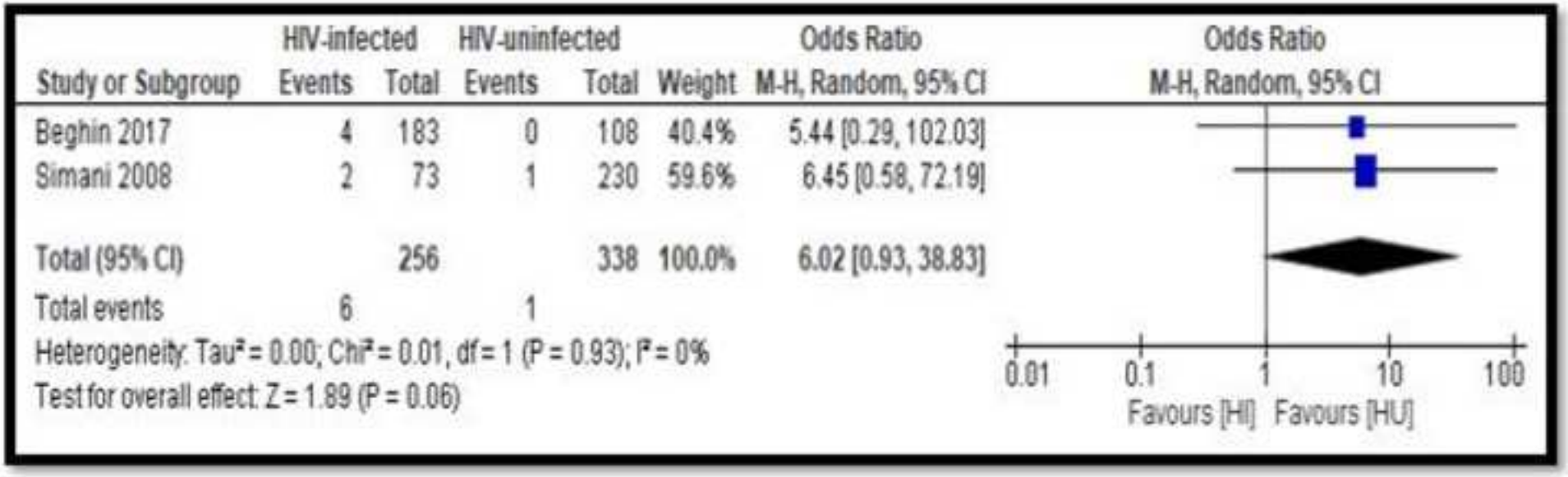

Figure: 6: Forest plot of comparison: Vaccine effectiveness comparing HIV-infected and HIV-uninfected - Hepatitis B vaccine, outcome: HBV/Hepatitis B vaccine

Table 1

Table 1: Characteristics of included studies

Participants						Intervention					Control				
1st Author & Year	**Study period**	**Study design**	**Study country**	**Sample size (n=)**	**Participant age range**	**HIV status**	**% on ART**	**CD4 % or count**	**Age (median or mean)**	**Vaccine strain**	**HIV status**	**% on ART**	**CD4 % or count**	**Age (median or mean)**	**Vaccine strain**
Beghin 2017[27]	2014	Cross-sectional study	South Africa	291	5-15y	HI	NR	NR	9.1y	HBV	HU	-	-	9.0y	HBV
Cohen 2017[21]	2012-2014	Case-Control	South Africa	1716	≥6w	HI	58%	-	48-53w	PCV13	HU	-	-	36-37w	PCV13
Bar-Zeev 2016[25]	1997-2007	Case-control	Malawi	919	<5y	HEU	-	-	NA	RV	HU	-	-	NA	RV
Van-Dunem 2015[22]	2005-2006	Case-control	Angola	902	18m - 13y	HI	67%	NR	4.83y	BCG Connaught	HI	61%	NR	3.50y	-
Cohen 2014[19]	2010-2012	Case-Control	South Africa	1395	≥8w	HI	46%	NR	52-54w	PCV7	HU	-	-	38-39w	PCV7
Groome 2014[23]	2010-2012	Case-control	South Africa	1195	18w-23m	HEU	-	-	9m	Monovalent human RV	HU	-	-	10 m	Monovalent human RV
Feikin 2012[16]	2007-2009	RCT	Kenya, Ghana, Mali	29	4-12w	HI	NR	NR	17.1w	PRV	HI	NR	NR	17.0	Placebo
Steele 2011[19]	2005-2008	RCT	South Africa	100	6-10w (at dose 1)	HI	62%	2074	7w	RIX4414	HI	52%	2022	7w	Placebo
Simani 2008[28]	2003-2004	Cross-sectional study	South Africa	303	5-24m	HI	NR	NR	8.7m	HBV	HU	-	-	11.9m	HBV
Madhi 2007[17]	2001 - 2005	Post RCT	South Africa	39836	5.57-5.80y	HI	22.5%	493; 627	5.80y; 5.68y	PCV9	HU	-	-	5.68y; 5.57y	Placebo
Madhi 2005[18]	1998 - 2001	RCT	South Africa	39836	28-84d	HI	NR	NR	NA	PCV9	HU	-	-		Placebo
Klugman 2003[15]	1998 - 2001	RCT	South Africa	39836	28-84d	HI	NR	NR	NA	PCV9	HU	-	-	7w	Placebo
Madhi 2002[26]	1997-2000	Cohort	South Africa	19267	<1y	HI	NR	NR	NR	HibCV	HU	-	-	NR	HibCV
Bhat 1993[24]	1991	Case-control	Zambia	270	1m-14y	HI	NR	NR	NR	BCG	HU	NR	NR	NR	BCG

HI - HIV-infected; HEU - HIV-exposed uninfected; HU - HIV-uninfected; NR- not reported; m- month; w – week; d- day; y- year; RCT – randomized controlled trial; HBV – Hepatitis B vaccine; HibCV- *haemophilus influenzae* b conjugate vaccine; PCV7 – 7-valent pneumococcal conjugate vaccine; PCV9 – 9-valent pneumococcal conjugate vaccine; PCV13 – 13-valent pneumococcal conjugate vaccine; BCG - Bacillus Calmette–Guérin; PRV – pentavalent rotavirus

Table 2: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (RCTs)

Patient or population: HIV-infected, HIV-exposed and HIV-uninfected children

Intervention: Vaccines

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	**Risk with vaccines**			
HI/PRV/RVGE	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 2.81** (0.12 to 63.83)	29 (1 RCT)	⨁⨁◯◯ LOW [a]
HI/RIX4414/RVGE	80 per 1,000	**80 per 1,000** (21 to 270)	**RR 1.00** (0.26 to 3.78)	100 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
HI/PCV9/severe pneumonia	280 per 1,000	**233 per 1,000** (205 to 266)	**RR 0.83** (0.73 to 0.95)	2577 (1 RCT)	⨁⨁⨁⨁ HIGH
HU/PCV9/severe pneumonia	36 per 1,000	**32 per 1,000** (28 to 36)	**RR 0.89** (0.80 to 1.00)	37259 (1 RCT)	⨁⨁⨁⨁ HIGH
HI/PCV9/Total IPD	26 per 1,000	**18 per 1,000** (11 to 30)	**RR 0.68** (0.40 to 1.14)	2577 (1 RCT)	⨁⨁⨁⨁ HIGH
HU/PCV9/Total IPD	1 per 1,000	**0 per 1,000** (0 to 0)	not estimable	37259 (1 RCT)	⨁⨁⨁⨁ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **HI:** HIV-infected; **PRV:** Pentavalent rotavirus vaccine; **RVGE**: Rotavirus gastroenteritis; **HU**: HIV-uninfected**; PCV9**: 9-valent pneumococcal conjugate vaccine**; IPD:** Invasive pneumococcal disease

Explanation: a. A wide confidence interval of the estimate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3: Summary of findings table for the efficacy of vaccines in HIV-infected, HIV-exposed and HIV-uninfected children (Observational studies)

Patient or population: HIV-infected, HIV-exposed and HIV-uninfected children

Intervention: Vaccine

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	**Risk with vaccine**			
HBV/Hepatitis B vaccine	3 per 1,000	**18 per 1,000** (3 to 103)	**OR 6.02** (0.93 to 38.83)	594 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]
HI/BCG/Tuberculosis	**Low**		**OR 1.00** (0.22 to 4.56)	36 cases 18 controls (1 observational study)	⨁◯◯◯ VERY LOW [b,c]
	0 per 1,000	**0 per 1,000** (0 to 0)			
HU/BCG/Tuberculosis	**Low**		**OR 0.41** (0.18 to 0.92)	60 cases 116 controls (1 observational study)	⨁◯◯◯ VERY LOW [b,c]
	0 per 1,000	**0 per 1,000** (0 to 0)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio**; BCG**: Bacillus Calmette–Guérin

Explanations: a. Confounders were not taken into account and unclear about the selection of study participants; b. A wide confidence interval around the estimate of the effects; c. Confounders not taken into account

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4

Table 4: Reported risk ratios and vaccine efficacy for vaccine-preventable diseases outcomes in vaccinated vs. non-vaccinated participants in randomised-controlled trials

Study ID (year)	Doses	Experimental recipients/vaccine	Control recipients/vaccine	Vaccine efficacy (%)	Disease of interest
Klugman 2003[15]	3	HI/PCV9	HI/placebo	53 (21 to 73)	First episodes of invasive pneumococcal disease
Klugman 2003[15]	3	HU/PCV9	HU/placebo	42 (-28 to 75)	
Klugman 2003[15]	3	HI/PCV9	HI/placebo	13 (-7 to 29)	First episodes of radiologically confirmed pneumonia
Klugman 2003[15]	3	HU/PCV9	HU/placebo	20 (2 to 35)	
Madhi 2005[17]	3	HI/PCV9	HI/placebo	17 (5, 27)	WHO-defined severe pneumonia
Madhi 2005[17]	3	HU/PCV9	HU/placebo	11 (1, 20)	
Madhi 2007[18]	3	HI/PCV9	HI/placebo	32 (-14, 60)	Total vaccine serotype invasive pneumococcal disease
Madhi 2007[18]	3	HU/PCV9	HU/placebo	78 (34, 92)	
Steele 2011[19]	3	HI/ RIX4414	HI/placebo	0 (-278, 74)	Acute rotavirus diarrhoea
Feikin 2012[16]	3	HI/PRV	HI/placebo	-181 (-6283, 88)	

Table 5

Table 5: Calculated vaccine efficacy and effectiveness for various vaccine outcomes

Outcomes	Number of studies	Experimental group	Control group	Relative effects	Study references
Hepatitis B virus infection	2	HI/HBV	HU/HBV	OR = 6.02 (0.93, 38.83)	27,28
Rotavirus gastroenteritis	1	HI/PRV	HI/Placebo	RR = 2.81 (0.12, 63.83)	16
Rotavirus gastroenteritis	1	HI/RIX4414	HI/Placebo	RR = 1.00 (0.26, 3.78)	19
Severe pneumonia	1	HI/PCV9	HI/Placebo	RR = 0.83 (0.73, 0.95)	17
Severe pneumonia	1	HU/PCV9	HU/Placebo	RR = 0.89 (0.80, 1.00)	17
Total Invasive Pneumococcal Disease	1	HI/PCV9	HI/Placebo	RR = 0.68 (0.40, 1.14)	18
Total Invasive Pneumococcal Disease	1	HU/PCV9	HU/Placebo	RR = 0.22 (0.08, 0.66)	18
Tuberculosis	1	HI/BCG	HI/Unvaccinated	OR = 1.00 (0.22, 4.56)	24
Tuberculosis	1	HU/BCG	HU/Unvaccinated	OR = 0.41 (0.18, 0.92)	24

BCG- Bacillus Calmette–Guérin vaccine; HI- HIV-infected; HU- HIV-uninfected; HBV – Hepatitis B virus; PCV – pneumococcal conjugate vaccine; PRV- pentavalent rotavirus; OR- odds ratio; RR- risk ratio

Table 6

Table 6: Reported vaccine effectiveness against vaccine-preventable diseases in observational studies

Study ID (year)	Vaccine type	Doses	HIV status	Vaccine effectiveness (%)	Adjusted vaccine effectiveness (%)	Disease of interest
Bhat (1993)[24]	BCG	1	HI	0 (−360 to 78)		Tuberculosis
		1	HU	59 (8 to 82)		
Madhi (2002)[26]	HibCV	3	HI	43.9 (76.1 to 82.1)		Invasive Hib disease
		3	HU	96.5 (74.4 to 99.5)		
Groome (2014)[23]	Monovalent RV	2	HEU		58% (16 to 79)	Acute rotavirus diarrhea
		2	HU		52% (23 to 70)	
Cohen (2014)[20]	PCV7	≥3	HI	43 (−108 to 85)	57 (−371 to 96)	Invasive pneumococcal disease
		≥3	HU	57 (−100 to 91)	90 (14 to 99)	
Van-Dunem (2015)[22]	BCG Connaught	1	HI	8 (−26 to 32)	30 (−75 to 72)	Tuberculosis
Bar-Zeev (2016)[25]	Monovalent RV	2	HEU		42.2% (−106.9 - 83.8)	Acute rotavirus diarrhea
		2	HU		60.5% (13.3–82.0)	
Cohen (2017)[21]	PCV13	≥2	HI (overall)	26% (–98 to 72)	17% (–304 to 80)	Invasive pneumococcal disease
		≥2	HI with severe immunosuppression	–42% (–723 to 76)	–104% (–1433 to 73)	
		≥2	HI with no severe immunosuppression	75% (–31 to 95)	66% (–94 to 94)	
		≥2	HU (overall)	83% (61 to 92)	78% (46 to 91)	
		≥2	HEU	91% (60 to 98)	87% (38 to 97)	